REMARKS

Claims 4, 14, 21, 22, 47-49, 64, 65, 73-82, and 127-142 were previously canceled. Claim 12 is currently canceled. Claims 1, 5, 16-18, 20, 23, 25-19, 33-36, 50-63, 66-72, 82-126, 143, and 152-164 have been withdrawn as being directed towards non-elected subject matter. Applicants reserve the right to file divisional or continuing applications directed towards the canceled subject matter. Claim 7 is currently amended. Support for the amendment can be found throughout the specification, for example at page 38, lines 25-28; page 44, lines 3-5; page 47, lines 14-15 (paragraphs [0173], [0195] and [0214] of the published application) and the claims as originally filed. No new matter has been added. Claims 1-3, 5-13, 15-20, 23-46, 50-63, 66-72, 83-126, and 143-166 are currently under consideration.

Rejections Under 35 U.S.C. §112, First Paragraph

Claims 2, 3, 6-13, 15, 19, 30-32, 144-151, 165, and 166 are rejected under 35 U.S.C. §112, first paragraph as failing to comply with the enablement requirement. Specifically, the Examiner states the while the specification is enabling for:

> (1) orally administering to said first mouse colitis extracted proteins (CEP) prepared from colons that were removed from TNBS-induced-colitis mice, cut into small strips, mechanically homogenized, filtered through a 40 mm nylon cell strainer, and the colitis extract supernatant isolated from intact cells via centrifugation;
>
> (2) obtaining 0.5 x 10^6 liver associated lymphocytes and 2.5 x 10^6 splenocytes from a second mouse that had been treated with TNBS to induce colitis and had been orally administered CEP prepared as in step (1);
>
> (3) adding to a culture of the 0.5 x 10^6 liver associated lymphocytes and 2.5 x 10^6 splenocytes from step (2) antigen presenting cells and CEP as in step (1);
>
> (4) optionally adding to said culture IL4, IL-10, TGFβ, IL 18 or IL 15;
>
> (5) administering the cultured cells of step (3) to the first mouse in

need of such treatment to modulate the Th1/Th2 balance towards anti-inflammatory cytokine producing cells, resulting in an increase in the quantitative ration between any one of IL4 and IL 10 to IFNγ

does not reasonably provide enablement for

a method for the treatment of any immune-related or immune-mediated disorders or disease in any mammalian subject in need of such treatment, by manipulating any or all NKT cell population(s) of said subject, wherein manipulation of said NKT cell population(s) results in modulation of the Th1/Th2 cell balance toward anti-inflammatory cytokine producing cells, said modulation being mediated by any components, cells, tissues or organs of said subject's or another subject's immune system, essentially for the reasons of record put forth in the Office Action mailed September 9, 2008:

See Office Action pages 2-3.

35 U.S.C. §112, first paragraph requires that a specification enable one skilled in the art to make and use the claimed invention. A specification fails to meet this requirement if the specification fails to provide sufficient information regarding the claimed subject matter to enable a skilled artisan to make and use the claimed invention. "However, to comply with 35 U.S.C. §112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.' *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338, 68 USPQ2d 1940, 1944 (Fed. Cir. 2003)." (MPEP §2164). To determine if sufficient information is provided, one must inquire whether the claimed invention can be practiced without undue experimentation. MPEP §2164.01. That some experimentation may be required is not fatal because the issue is whether the experimentation is undue. *In re Vaeck*, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991).

Applicants respectfully traverse the rejection and assert that the claims are enabled for the full scope of the claims. In evaluating the experimental results summarized in Table 6, the Examiner states that the exact value of the IFNγ/IL10 ratio is critical because it represents the "very measure of treatment success recited..." See Office Action page 4. As explained in detail in the previous response, the absolute numbers of the ratio of IFNγ/IL10 that result from treatment are as important as the directionality that is obtained in the response. Thus, although

E"2 indicates a ratio of 52:1 was achieved (using the 0 detection level of IFNγ being considered to be at least 1 unit), only 52 units of IL10 response are detected after exposure to TNBS. In comparison, with E"5 (an ex vivo exposure of the cells to antigens), the IL10 response (the anti-inflammatory immune response) is boosted. These results illustrate the very purpose of the experiment since, as discussed above, the specification described:

> As shown in Table 6, culturing NK1.1+Tcells in the presence of disease associated antigens (subgroup E"5) leads to cytokine pattern that is similar to that of tolerized cells **as manifested by increase IL10 production**. (emphasis added)

See Specification, U.S. Patent Application Publication No. 2005/0069546, paragraph [0356].

The ratio represents an evaluation of IFNλ to insure that there is a "net profit" for anti-inflammatory responses (as judged by IL10 levels) compared to an induction of pro-inflammatory responses (as judged by IFNγ levels). Therefore, the change that that takes place by treatment via *ex vivo* exposure to antigens (education) indicates that although the IFNγ increased by 38 (38 in E"5 – 0 in E"2), this change was accompanied by an increase in IL10 of 288 (340 in E"5 – 52 in E"2). The directionality of the change was 288/38 in favor of IL10, *i.e.,* a directionality that results in an increased anti-inflammatory response. The increased response was considered by the inventors to be beneficial, very similar to how E"3 showed an increase in IL10 (although without detection of an increase in IFNγ) by induction of oral toleration before isolation of the NKT cells. In essence, the inclusion of IFNγ in addition to IL10 is a control which insures that the measured effects are attributable to an anti-inflammatory directionality as opposed to a contemporaneous indiscriminate induction of equal or even higher levels of pro-inflammatory responses. These pro-inflammatory responses would negate beneficial responses otherwise provided by the induction of the anti-inflammatory responses. One of skill in the art would appreciate that the results of E"5 indicate that administration of antigen-exposed NKT cells will produce a beneficial result.

The Examiner states on page 5 of the Office Action:

> However, neither the instant specification nor the art seem to recognize what

> particular biomolecular constituent of "colitis extracted protein" is sufficient to mediate its biological effects when administered orally or ex vivo as put forth in the previous Office Action at page 11, 3rd-4th paragraphs.
>
> Given this uncertainty as to the active agent(s), the particular steps used to prepare the "colitis extracted protein" exemplified in the instant specification will determine the composition of this extract. For example, an extract prepared by collecting the fluid phase from colon cellular material will have a different composition from an extract prepared by treating colon cellular material with a mild detergent and collecting the soluble and/or insoluble fraction, which will have a different composition from an extract prepared by sonicating colon cellular material and collecting this soluble and/or insoluble fraction etc.

Applicants respectfully assert that one of skill in the art could utilize the methods described in the specification, or other methods known in the art, to derive effective extracts. Furthermore, the presently claimed invention does not require the identification of the "particular biomolecular constituent" of "colitis extracted protein". Although the "particular biomolecular constituent" may vary according to the extraction method, determination of this constituent is merely a question of optimization. The Examiner has acknowledged that determination of the constituent could be as simple as testing both soluble an insoluble fractions of a cell extract, scarcely a call for "undue experimentation".

The Examiner states that the specification provides "...only a single example of obtaining NKT cells, in particular, NK1,1+ NKT cells, from a mouse and ex vivo 'educating' the NKT cells in the presence of 'colitis extracted proteins' obtained from a mouse with TNBS induced colitis." See Office Action page 5. The Examiner then contends that one of skill in the art would not have the ability to extend the method to the ex vivo education or any or all human NKT cells to treat any immune-related disorder or disease. See Office Action pages 5-6.

In response, Applicants respectfully submit that the Federal Circuit has stated on several occasions that an actual reduction to practice is unnecessary to satisfy the written description requirement. For example:

> We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an

> actual reduction to practice. Constructive reduction to practice is an established method of disclosure, but the application must nonetheless "describe the claimed subject matter in terms that establish that [the applicant] was in possession of ...the claimed invention, including all of the *elements and limitations*.

University of Rochester v. G.D. Searle & Co., 358 F.3d 916, 926 (Fed. Cir. 2004). In addition, the use of "murine NKT 1.1 T cells" or "murine TNBS colitis," as described in the specification, should not limit one to extrapolate that similar effects may be achieved with human NKT cells. Murine NKT cells are considered by one of skill in the art to be an acceptable model to study the immunological effects that would occur in human NKT cells. The large amount of research devoted to such studies would have been impossible without this model. Similarly, the TNBS colitis model is widely used as an animal model of human colitis. The availability this model as a research tool is possible because of its ability to be adapted to human disease processes-- there is no particular utility or desire among researchers for curing colitis conditions in mice. The use of animal models for the study and experimentation of processes and the development of proof of principles in therapeutic procedures for humans is a time honored method of practice for research as well as for clinical trials.

The Examiner cites to Doherty in stating "...there is no a priori reason to believe that the claimed ex vivo education of NKT cells, for example in claims 6 or 7, is anything more than one mechanism to activate NKT cells, and as taught by Doherty human CD56+ NKT cells produce anti-inflammatory Th1 type cytokines upon activation (see previous Office Action page 13-14)." See Office Action page 6. In addition, the Examiner cites to Kaneko in stating "...there seems to be no reason why IL-4 producing NKT cells which induce hepatitis by killing liver cells wouldn't perpetuate hepatitis by killing yet more liver cells." See Office Action page 6. Applicants respectfully assert that results achieved by the use of an unsegregated population of NKT cells is necessarily repudiated by papers that are limited to specific subpopulations. The existence of subpopulations that may act differently from the whole population is fairly self-evident, but the significance of this for comparison with an unsegregated population of NKT cells is not necessarily apparent and can only be derived by ungrounded speculation. Furthermore, under the Examiner's interpretation, the Doherty and Kaneko references would

teach that the anti-inflammatory results achieved by the inventor would be unachievable. Reconciliation of this statement with the results describe in the specification is possible by the conclusion that results of subpopulations do not predict results of the population as a whole.

The Examiner states on page 7 of the Office Action that the specification is enabled for the adhesion molecule E-selectin, but not for LFA-1 and ICAM-1. Applicants respectfully disagree and assert that the claims are fully enabled for all of the listed adhesion molecules. However, solely in an effort to promote prosecution, claim 7 has been amended to read "the adhesion molecule selectin."

The Examiner states that the Maragalit does not convincingly demonstrate that the disclosure of Applicants' invention enables the breadth of the claims. See Office Action page 8. Applicants respectfully assert that the cited portions of the previously submitted amendment ("It is apparent that the method did work but the success rate was not as high as would be desired") indicates that the method was still successful. This properly supports a proof of principle and that the inventors were in possession of the invention. The fact that a degree of optimization may be required does not render the claims non-enabled. That some experimentation may be required is not fatal because the issue is whether the experimentation is undue. *In re Vaeck*, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). The claims currently recite "A method of treatment" and do not specifically require a complete success rate. Clinical trials demand a very particular level of success, whereas experiments supporting the potential effectiveness of a novel method do not require such a showing. The Examiner further points to a disclosure in Margalit which states "its efficacy needs to be proven" as further proof that he claims are not enabled. Applicants respectfully contend that this statement reflects the particular level of efficaciousness required to established a developed, mature pharmacological agent after an optimization program, a standard that does not need to be met for the present claims.

Contrary to the Examiner's contentions, the specification provides adequate instruction to allow one of skill in the art to make and use the invention. As acknowledged by the Examiner, the oral administration of CEP did show the alleviation of symptoms. In addition, the specification teaches accordance of effects between NKT cells that have undergone *in vivo* training by oral tolerization and NKT cells that have undergone *ex vivo* training. The

Experimental results as described in the specification indicate that NKT cells which have been trained by either method are effective in ameliorating inflammatory markers and producing a shift in the Th1/Th2 balance. In addition, the present invention is not limited to a particular subset of NKT cells, nor does the invention require one to either identify the particular component(s) that induced both in vivo and *ex vivo* training of the NKT cells. That some experimentation may be required to practice an invention is not fatal to patentability. Instead, one must inquire whether the claimed invention can be practiced without *undue* experimentation. Here, Applicants' specification provides adequate guidance to practice the invention without undue experimentation. Withdrawal of the rejection is respectfully requested.

Rejection Under 35 U.S.C. §102(b)

Claims 2, 3, 6-13, 15, 19, 32, 144-151, 165, and 166 are rejected under 35 U.S.C. §102(b) as being anticipated by the '986 application. The Examiner states that the '986 application teaches the claimed invention, in particular a method of treating Crohn's disease. Office Action page 9.

Applicants respectfully traverse the rejection. For a rejection under 35 U.S.C. §102 to be properly made and sustained, the art cited in that rejection must disclose each and every element of the claim(s) called out in the rejection. MPEP §2131. The present application is a continuation-in-part of U.S. Patent Application No. 10/451/811, filed June 25, 2003, which is the national stage filing PCT/IL01/01197, filed December 24, 2001. WO/02051986 is the international publication of PCT/IL01/01197. The Examiner states that the present claims are directed to subject matter disclosed in WO/02051986. Thus, the subject matter of the rejected claims properly claim priority to PCT/IL01/01197 (filing date December 24, 2001). WO/02051986 is therefore not a proper 102(b) reference. Withdrawal of the rejection is respectfully requested.

CONCLUSION

Applicants respectfully submit that all claims are in condition for allowance. Early notification of a favorable consideration is respectfully requested. In the event any issues remain, Applicants would appreciate the courtesy of a telephone call to their counsel at the number listed below to resolve such issues and place all claims in condition for allowance.

The Office is hereby authorized to charge any additional fees or credit any overpayments under 37 C.F.R. § 1.16 or § 1.17 to the deposit account number 50-0525.

Respectfully submitted,

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Dated: January 11, 2010

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